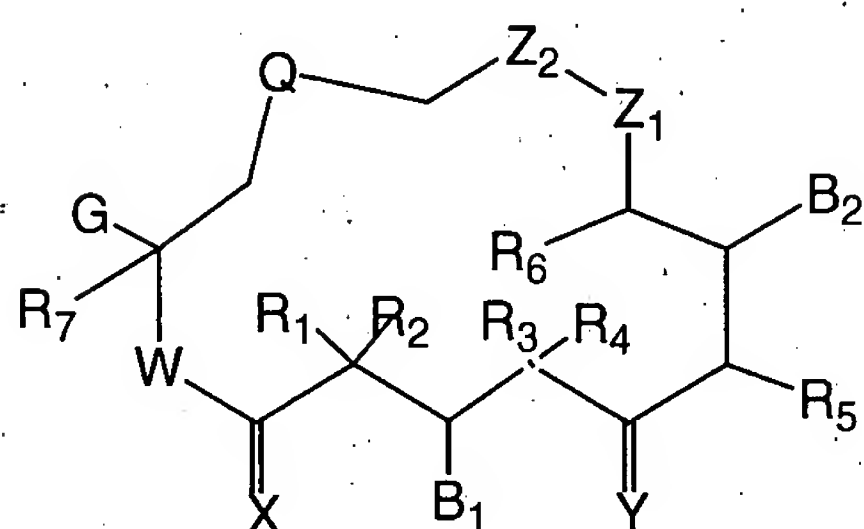


## What Is Claimed Is:

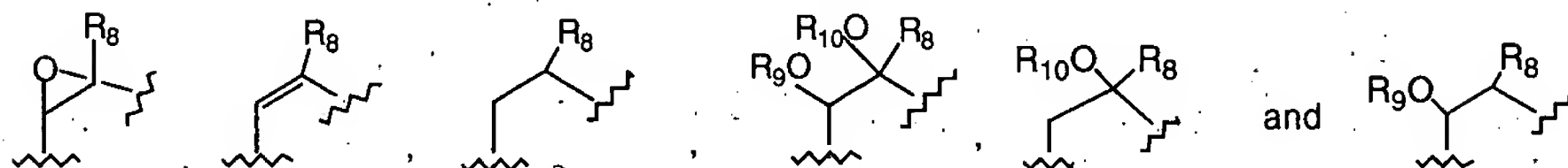
- (4) 1. A method for the treatment of proliferative diseases, including cancer, which comprises administering to a mammalian specie in need thereof a synergistically, therapeutically effective amount of (1) at least one anti-proliferative agent(s) and 2) a compound of formula I,

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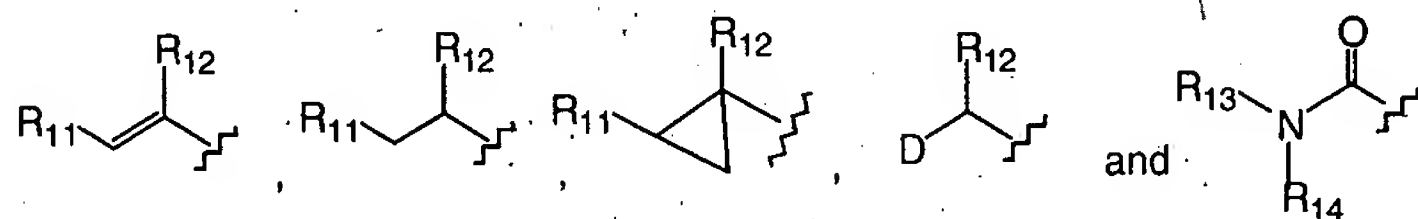
wherein:

- 15 Q is selected from the group consisting of



G is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo,

20

W is O or N R<sub>15</sub>;

X is O or H, H;

Y is selected from the group consisting of O; H, OR<sub>16</sub>

- 25 ; OR<sub>17</sub>, OR<sub>17</sub>; NOR<sub>18</sub>; H, NHOR<sub>19</sub>; H, NR<sub>20</sub>R<sub>21</sub>; H, H; and CHR<sub>22</sub>;

wherein OR<sub>17</sub>, OR<sub>17</sub> can be a cyclic ketal;Z<sub>1</sub> and Z<sub>2</sub> are independently selected from the group

consisting of  $\text{CH}_2$ , O,  $\text{NR}_{23}$ , S, and  $\text{SO}_2$ , wherein only one of  $\text{Z}_1$  and  $\text{Z}_2$  can be a heteroatom;

$\text{B}_1$  and  $\text{B}_2$  are independently selected from the group consisting of  $\text{OR}_{24}$ ,  $\text{OCOR}_{25}$ , and  $\text{O}-\text{C}(=\text{O})-\text{NR}_{26}\text{R}_{27}$ , and when  $\text{B}_1$  is H and Y is OH, H, they can form a six-membered ring ketal or acetal;

D is selected from the group consisting of  $\text{NR}_{28}\text{R}_{29}$ ,  $\text{NR}_{30}\text{COR}_{31}$  and saturated heterocycle;

$\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$ ,  $\text{R}_5$ ,  $\text{R}_6$ ,  $\text{R}_7$ ,  $\text{R}_{13}$ ,  $\text{R}_{14}$ ,  $\text{R}_{18}$ ,  $\text{R}_{19}$ ,  $\text{R}_{20}$ ,  $\text{R}_{21}$ ,  $\text{R}_{22}$ ,  $\text{R}_{26}$  and  $\text{R}_{27}$  are independently selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when  $\text{R}_1$  and  $\text{R}_2$  are alkyl can be joined to form a cycloalkyl, and when  $\text{R}_3$  and  $\text{R}_4$  are alkyl can be joined to form a cycloalkyl;

$\text{R}_9$ ,  $\text{R}_{10}$ ,  $\text{R}_{16}$ ,  $\text{R}_{17}$ ,  $\text{R}_{24}$ ,  $\text{R}_{25}$  and  $\text{R}_{31}$  are independently selected from the group consisting of H, alkyl, and substituted alkyl;

$\text{R}_8$ ,  $\text{R}_{11}$ ,  $\text{R}_{12}$ ,  $\text{R}_{28}$ ,  $\text{R}_{30}$ ,  $\text{R}_{32}$ , and  $\text{R}_{33}$  are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl and heterocyclo;

$\text{R}_{15}$ ,  $\text{R}_{23}$  and  $\text{R}_{29}$  are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo,  $\text{R}_{32}\text{C}=\text{O}$ ,  $\text{R}_{33}\text{SO}_2$ , hydroxy, O-alkyl or O-substituted alkyl; and

pharmaceutically acceptable salts thereof and any hydrates, solvates or geometric, optical and stereoisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

$\text{R}_1$ ,  $\text{R}_2$  and  $\text{R}_7$  are H; and

$\text{R}_3$ ,  $\text{R}_4$  and  $\text{R}_6$  are methyl; and

$\text{R}_8$  is H or methyl; and

$\text{Z}_1$  and  $\text{Z}_2$  are  $\text{CH}_2$ ; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl;

and

Q is as defined above  
are excluded.

- 5 2. The method according to Claim 1 wherein the antiproliferative agent is administered following administration of the Formula I compound.
- 10 3. The method according to Claim 1, wherein the antiproliferative agent is administered prior to the administration of the Formula I compound.
- 15 4. The method according to Claim 1 wherein the antiproliferative agent is administered simultaneously with the formula 1 compound.
- 20 X 5. The method according to Claim 1 for the treatment of cancerous solid tumors.
- X 6. The method according to Claim 1 for the treatment of refractory tumors.
- 25 X 7. The method according to Claim 1 wherein the anti-proliferative agent is selected from the group consisting of a microtubule-stabilizing agent, a microtubule-disruptor agent, an alkylating agent, an anti-metabolite, epidophyllotoxin, an antineoplastic enzyme, a topoisomerase inhibitor, procarbazine, mitoxantrone, 30 inhibitors of cell cycle progression, radiation and a platinum coordination complex.
8. The method according to Claim 1 wherein the anti-proliferative agent is selected from the group consisting 35 of an anthracycline drug, a vinca drug, a mitomycin, a

bleomycin, a cytotoxic nucleoside, a taxane, an  
epothilone, discodermolide, a pteridine drug, a diynene,  
an aromatase inhibitor and a podophyllotoxin.

5 9. The method according to Claim 1, wherein the Compound  
of Formula I is [1S-1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-  
7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-  
methyl-4-thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
10 proliferative agent is Compound 2.

15 10. The method according to Claim 2, wherein the  
Compound of Formula I is [1S-  
1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
proliferative agent is Compound 2.

20 11. The method according to Claim 1, wherein the  
Compound of Formula I is [1S-  
1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-4-aza-17-  
25 oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
proliferative agent is Compound 3.

30 12. The method according to Claim 2 wherein said  
compound of Formula I is [1S  
1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
proliferative agent is Compound 3.

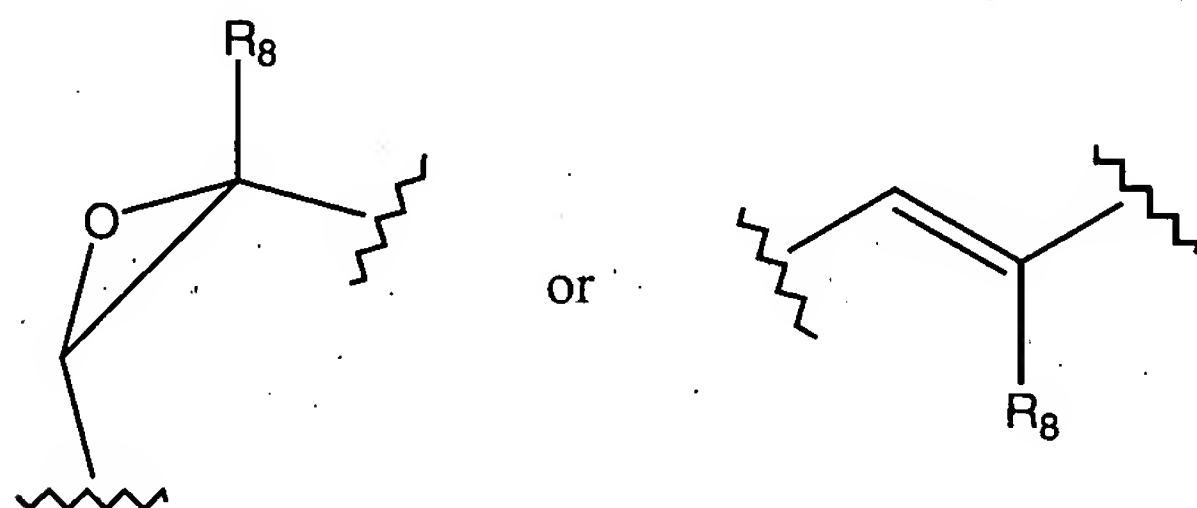
35

13. The method according to Claim 1 wherein said compound of Formula I is [1S 1R\*, 3R\*(E), 7R\*, 10S\*, 11R\*, 12R\*, 16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.
14. The method according to Claim 2 wherein said compound of Formula I is [1S 1R\*, 3R\*(E), 7R\*, 10S\*, 11R\*, 12R\*, 16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.
15. The method according to Claim 1, wherein said compound of Formula I is [1S 1R\*, 3R\*(E), 7R\*, 10S\*, 11R\*, 12R\*, 16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Cisplatin.
16. The method according to Claim 3, wherein said compound of Formula I is [1S 1R\*, 3R\*(E), 7R\*, 10S\*, 11R\*, 12R\*, 16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Cisplatin.
17. The method according to Claim 1, wherein said method comprises the administration of Compound 1 and Carboplatin.
18. The method according to Claim 1, wherein said method

comprises the administration of Compound 1 and doxorubicin.

19. The method according to claim 1, said method comprising the administration of Compound 1 and CPT-11.

20. The method according to claim 1, wherein Q in said Formula I compound is



10

X is O;

Y is O;

Z<sub>1</sub> and Z<sub>2</sub> are, independently, CH<sub>2</sub>; and

W is NR<sub>15</sub>.

15

21. The method according to Claim 6, wherein said compound of Formula I is selected from the group consisting of:

20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

30 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-

pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-dione;

- 5 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-dione;
- 10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 20 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxo-13-cyclohexadecene-2,6-dione;
- 25 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxo-13-cyclohexadecene-2,6-dione;
- 30 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;
- 35 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-

8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

- 5 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;
- 20 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;
- 25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 35 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-



oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-

5 thiazolyl)ethenyl]-4-aza-17-

oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-16-[1-methyl-2-(2-methyl-4-

10 thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-

tetramethyl-16-[1-methyl-2-(2-methyl-4-

thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

15

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-

4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-

thiazolyl)ethenyl]-4-aza-17-

oxabicyclo[14.1.0]heptadecane-5,9-dione;

20

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-

4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-

thiazolyl)ethenyl]-4-aza-17-

oxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-

1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl-4-

thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

30

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-1,5,5,7,9-

pentamethyl-16-[1-methyl-2-(2-methyl-4-

thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-

35 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-

thiazolyl)ethenyl]-13-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
5 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-13-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
10 pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
15 tetramethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
20 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-14-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
25 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-14-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
30 pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
35 tetramethyl-16-[1-methyl-2-(2-methyl- 4-

thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

5 [1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

10 [1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

15 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione; and

30 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione; and pharmaceutically acceptable salts, solvates and hydrates thereof.

22. The method as claimed in Claim 7, wherein said Compound of Formula I is selected from the group consisting of:

- 5 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-dione;
- 20 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-dione;
- 25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 35 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-

pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxo-13-cyclohexadecene-2,6-dione;

5 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxo-13-cyclohexadecene-2,6-dione;

10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

15 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxo-13-cyclohexadecene-2,6-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl- 4-

35

thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
5 thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-  
5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
10 thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-  
5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
15 thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
20 thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
25 thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
tetramethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

30 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione;

35

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-  
1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

10 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-1,5,5,7,9-  
pentamethyl-16-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

15 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-13-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-13-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-16-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

30 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
tetramethyl-16-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

35 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-

thiazolyl)ethenyl]-14-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
5 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-14-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
10 pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
15 tetramethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

[1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-  
20 dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-  
dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-  
dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-  
25 dioxabicyclo[14.1.0]heptadecane-3-carboxamide;  
[4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-  
5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-  
cyclohexadecene-16-carboxamide;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-  
30 5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-  
16-carboxamide;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
35 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-



thiazolyl)cyclopropyl]-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
5 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)cyclopropyl]-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione; and

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
10 pentamethyl-16-[1-methyl-2-(2-hydroxymethyl- 4-  
thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione;  
and pharmaceutically acceptable salts, solvates and  
hydrates thereof.

15 23. A pharmaceutical composition for the treatment  
of cancer which comprises at least one anti-proliferative  
agent and a compound of Formula I as described in Claim  
1, and a pharmaceutically acceptable carrier.

20 24. The composition according to Claim 23 for the  
treatment of cancerous solid tumors.

25 25. The composition according to Claim 23 for the  
treatment of refractory tumors.

26. The composition according to Claim 23 wherein the  
antiproliferative agent is one or more agent selected  
from the group consisting of a microtubule-stabilizing  
agent, a microtubule-disruptor agent, an alkylating  
30 agent, an anti-metabolite, epidophyllotoxin, an  
antineoplastic enzyme, a topoisomerase inhibitor,  
procarbazine, mitoxantrone, inhibitors of cell cycle  
progression, a platinum coordination complex, an  
anthracycline drug, a vinca drug, CDK inhibitors, a  
35 mitomycin, a bleomycin, a cytotoxic nucleoside, a taxane,

compound 2, compound 3, an epothilone, discodermolide, a pteridine drug, a diyne, an aromatase inhibitor and a podophyllotoxin.

- 5 27. The composition according to Claim 23 wherein the compound of Formula I is selected from the group consisting of [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-
- 10 trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-
- 15 trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-
- 20 dione;
- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-
- 25 dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,14,17-
- 30 trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,14,17-
- 35 trioxabicyclo[14.1.0]heptadecane-5,9-dione;

5 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxo-13-cyclohexadecene-2,6-dione;

10 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxo-13-cyclohexadecene-2,6-dione;

15 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxo-13-cyclohexadecene-2,6-dione;

- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;
- 5 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;
- 20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;
- 25 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-
- 30 tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-
- 35 4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-

oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
5 thiazolyl)ethenyl]-4-aza-17-

oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-  
1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl- 4-  
10 thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-1,5,5,7,9-  
pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
15 thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-13-aza-4,17-

dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-13-aza-4,17-

dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
tetramethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

35

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-14-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-14-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-16-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

15

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
tetramethyl-16-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

20

[1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-  
dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-  
dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

25

[1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-  
dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-  
dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

30

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-  
5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-  
cyclohexadecene-16-carboxamide;

35

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-  
5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-  
16-carboxamide;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-  
thiazolyl)cyclopropyl]-4,17-  
5 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-  
thiazolyl)cyclopropyl]-4,17-  
10 dioxabicyclo[14.1.0]heptadecane-5,9-dione; and

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-16-[1-methyl-2-(2-hydroxymethyl-4-  
thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione;  
15 and pharmaceutically acceptable salts, solvates and  
hydrates thereof.

28. The composition according to Claim 26 wherein the  
20 pharmaceutically acceptable salt is selected from the  
group consisting of the hydrochloride salt, the  
methanesulfonic acid salt and the trifluoroacetic acid  
salt.

25 29. The composition according to Claim 26 wherein the  
formula I compound is [1S-  
1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-4-aza-17-  
30 oxabicyclo[14.1.0]heptadecane-5,9-dione or a  
pharmaceutically acceptable salt thereof and the anti-  
proliferative agent is Compound 2.

30. The composition according to Claim 26 wherein the  
35 antiproliferative agent is Compound 3 and the formula I



compound is [1S 1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*, 16S\*]]-  
 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-  
 methyl-4-thiazolyl)ethenyl]-4-aza-17-  
 oxabicyclo[14.1.0]heptadecane-5,9-dione or a  
 5 pharmaceutically acceptable salt thereof.

31. The composition according to Claim 26 wherein the  
 antiproliferative agent is Compound 5 and the formula I  
 compound is [1S 1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*, 16S\*]]-  
 10 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-  
 methyl-4-thiazolyl)ethenyl]-4-aza-17-  
 oxabicyclo[14.1.0]heptadecane-5,9-dione or a  
 pharmaceutically acceptable salt thereof.

15 32. The composition according to claim 26 wherein the  
 antiproliferative agent is cisplatin and the compound of  
 formula I is [1S 1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-  
 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-  
 methyl-4-thiazolyl)ethenyl]-4-aza-17-  
 20 oxabicyclo[14.1.0]heptadecane-5,9-dione.

33. The composition according to claim 23, wherein said  
 composition comprises Compound 1 and carboplatin.

25 34. The composition according to claim 23, wherein said  
 composition comprises Compound 1 and doxorubicin.

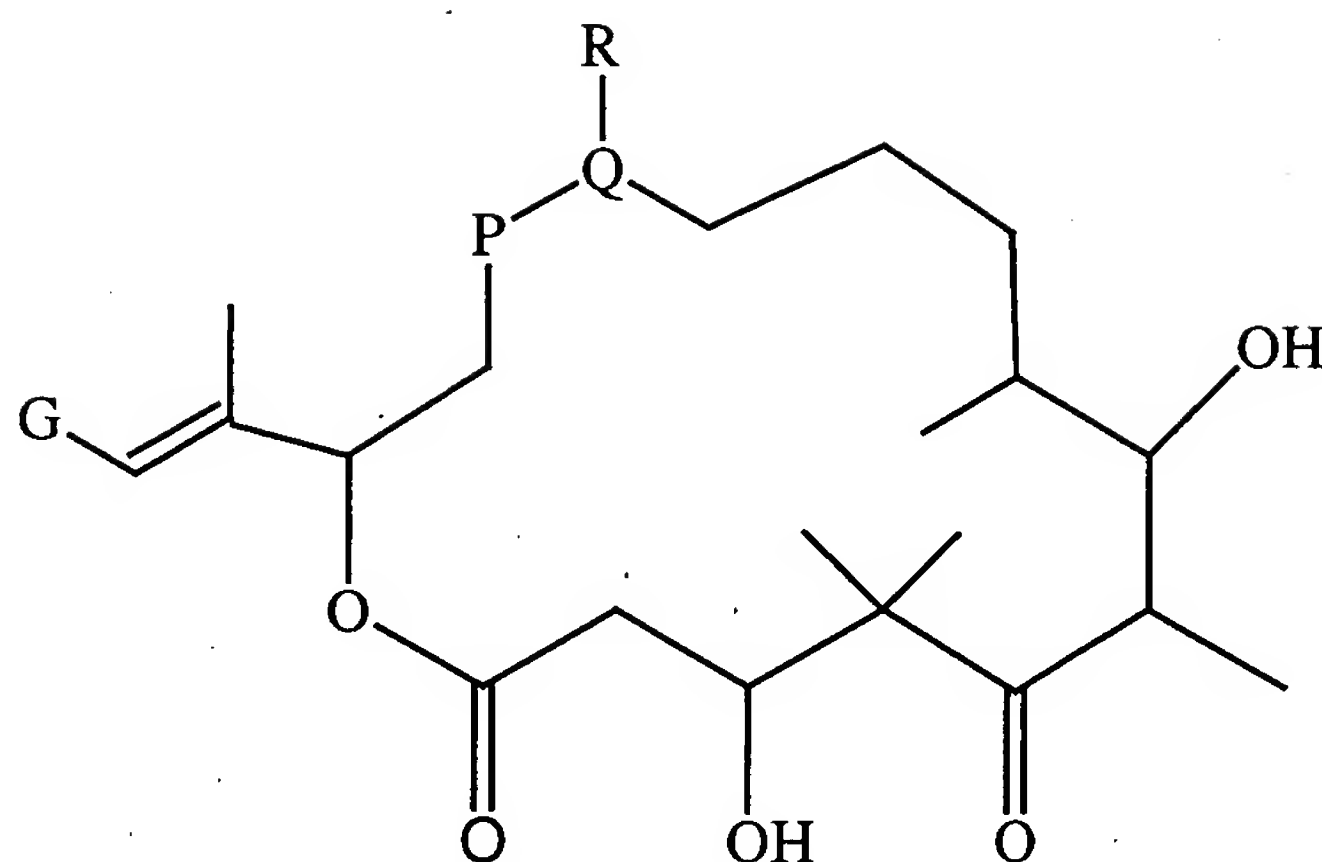
35. The composition according to claim 23, wherein said  
 composition comprises Compound 1 and CPT-11.

30

36. A method for the treatment of proliferative  
 diseases, including cancer, which comprises administering  
 to a mammalian specie in need thereof a synergistically,  
 therapeutically effective amount of (1) at least one  
 35 anti-proliferative agent(s) and (2) a compound of Formula



II:

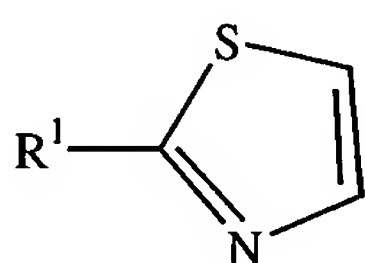


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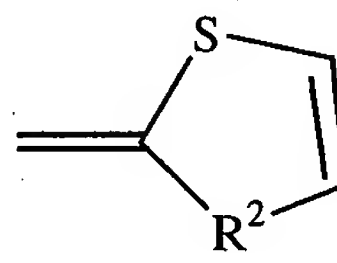
wherein:

P-Q is a C, C double bond or an epoxide;

G is



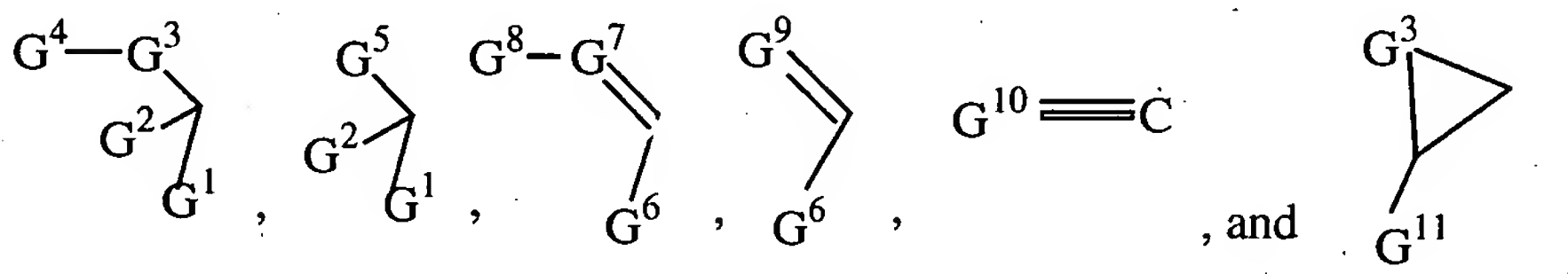
or



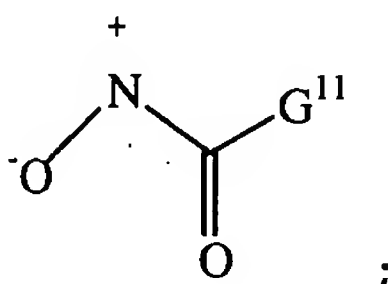
;

10

R is selected from the group of H, alkyl, and substituted alkyl;

R<sup>1</sup> is selected from the group consisting of

15

R<sup>2</sup> is

;

G<sup>1</sup> is selected from the group of H, halogen, CN, alkyl and substituted alkyl;G<sup>2</sup> is selected from the group of H, alkyl, and

substituted alkyl;

$G^3$  is selected from the group of O, S, and  $NZ^1$ ;

$G^4$  is selected from the group of H, alkyl, substituted alkyl,  $OZ^2$ ,  $NZ^2Z^3$ ,  $Z^2C=O$ ,  $Z^4SO_2$ , and optionally substituted glycosyl;

$G^5$  is selected from the group of halogen,  $N_3$ , NCS, SH, CN, NC,  $N(Z^1)_3^+$  and heteroaryl;

$G^6$  is selected from the group of H, alkyl, substituted alkyl,  $CF_3$ ,  $OZ^5$ ,  $SZ^5$ , and  $NZ^5Z^6$ ;

10  $G^7$  is  $CZ^7$  or N;

$G^8$  is selected from the group of H, halogen, alkyl, substituted alkyl,  $OZ^{10}$ ,  $SZ^{10}$ ,  $NZ^{10}Z^{11}$ ;

$G^9$  is selected from the group of O, S, -NH-NH- and -N=N-;

15  $G^{10}$  is N or  $CZ^{12}$ ;

$G^{11}$  is selected from the group of  $H_2N$ , substituted  $H_2N$ , alkyl, substituted alkyl, aryl, and substituted aryl;

$Z^1$ ,  $Z^6$ ,  $Z^9$ , and  $Z^{11}$  are independently selected from the group H, alkyl, substituted alkyl, acyl, and substituted acyl;

20  $Z^2$  is selected from the group of H, alkyl, substituted alkyl, aryl, substituted aryl, and heterocycle;

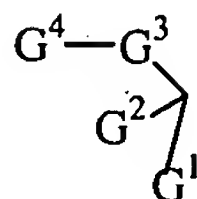
$Z^3$ ,  $Z^5$ ,  $Z^8$ , and  $Z^{10}$  are independently selected from the group H, alkyl, substituted alkyl, acyl, substituted acyl, aryl, and substituted aryl;

$Z^4$  is selected from the group of alkyl, substituted alkyl, aryl, substituted aryl, and heterocycle;

30  $Z^7$  is selected from the group of H, halogen, alkyl, substituted alkyl, aryl, substituted aryl,  $OZ^8$ ,  $SZ^8$ , and  $NZ^8Z^9$ ; and

$Z^{12}$  is selected from the group of H, halogen, alkyl, substituted alkyl, aryl, and substituted aryl;

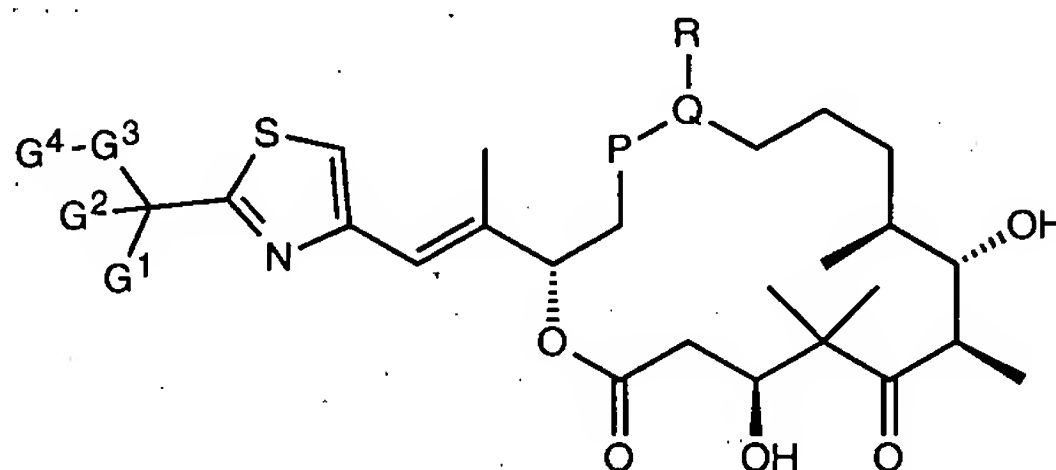
with the proviso that when  $R^1$  is



$G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  cannot simultaneously have the following meanings:

$G^1$  and  $G^2 = H$ ,  $G^3 = O$  and  $G^4 = H$  or  $Z^2C=O$  where  $Z^2 =$   
 5 alkyl group.

37. The method according to Claim 36 wherein the  
 10 compound has the general formula IIa



where the symbols have the following meaning:

P-Q is a C,C double bond or an epoxide,

15 R is a H atom or a methyl group,

$G^1$  is an H atom, an alkyl group, a substituted alkyl group or a halogen atom,

$G^2$  is an H atom, an alkyl group or a substituted alkyl group,

20  $G^3$  is an O atom, an S atom or an  $NZ^1$  group with

$Z^1$  being an H atom, an alkyl group, a substituted alkyl group, an acyl group, or a substituted acyl group, and

$G^4$  is an H atom, an alkyl group, a substituted alkyl group, an  $OZ^2$  group, an  $NZ^2Z^3$  group, a  $Z^2C=O$  group, a  $Z^4SO_2$

25 group or an optionally substituted glycosyl group with  $Z^2$  being a H atom, an alkyl group, a substituted alkyl group, an aryl group, a substituted aryl group or a heterocyclic group,

$Z^3$  an H atom, an alkyl group, a substituted alkyl group, an acyl group or a substituted acyl group, and  $Z^4$  an alkyl, a substituted alkyl, an aryl, a substituted aryl or a heterocyclic group,

5

with the proviso that  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  cannot have simultaneously the following meanings:  $G^1$  and  $G^2$  = H atom,  $G^3$  = O atom and  $G^4$  = H atom or  $Z^2C=O$  with  $Z^2$  = alkyl group.

10 38. The method of claim 36 wherein said compound of Formula II is [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-

15

39. The method according to Claim 36, wherein the antiproliferative agent is administered following administration of the Formula II compound.

20 40. The method according to Claim 36, wherein the antiproliferative agent is administered prior to administration of the Formula II compound.

25 41. The method according to Claim 36, wherein the antiproliferative agent is administered simultaneously with the Formula II compound.

42. The method according to Claim 36 for the treatment of cancerous solid tumors.

30

43. The method according to Claim 36 for the treatment of refractory tumors.

35 44. The method according to Claim 36 wherein the antiproliferative agent is selected from the group consisting

of a microtubule-stabilizing agent, a microtubule-disruptor agent, an alkylating agent, an anti-metabolite, epidophyllotoxin, an antineoplastic enzyme, a topoisomerase inhibitor, procarbazine, mitoxantrone,  
 5 radiation, a platinum coordination complex, anthracycline drug, a vinca drug, a mitomycin, inhibitors of cell cycle progression, a bleomycin, a cytotoxic nucleoside, a taxane, an epothilone, discodermolide, a pteridine drug, a diynene, an aromatase inhibitor and a podophyllotoxin.

10

45. The method according to Claim 37 wherein the anti-proliferative agent is selected from the group consisting of a microtubule-stabilizing agent, a microtubule-disruptor agent, an alkylating agent, an anti-metabolite,  
 15 epidophyllotoxin, an antineoplastic enzyme, a topoisomerase inhibitor, procarbazine, mitoxantrone, radiation, a platinum coordination complex, anthracycline drug, a vinca drug, a mitomycin, inhibitors of cell cycle progression, a bleomycin, a cytotoxic nucleoside, a  
 20 taxane, an epothilone, discodermolide, a pteridine drug, a diynene, an aromatase inhibitor and a podophyllotoxin.

46. The method according to Claim 36, wherein the Compound of Formula II is 1S-  
 25 [1R\*, 3R\* (E), 7R\*, 10S\*, 11R\*, 12R\*, 16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 2.

30

47. The method according to Claim 37, wherein the Compound of Formula II is 1S-  
 35 [1R\*, 3R\* (E), 7R\*, 10S\*, 11R\*, 12R\*, 16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-

dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 2.

48. The method according to Claim 36 wherein said compound of Formula II is 1S-

[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 3.

49. The method according to Claim 37 wherein said compound of Formula II is 1S-

[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 3.

50. The method according to Claim 36, wherein said compound of Formula II is 1S-

[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-

dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Cisplatin.

51. The method according to Claim 37, wherein said compound of Formula II is 1S-

[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-

dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Cisplatin.

52. The method according to Claim 36, wherein said compound of Formula II is 1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.

53. The method according to Claim 37, wherein said compound of Formula II is 1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.

54. The method according to Claim 36, wherein said method comprises the administration of Compound 4 and Carboplatin.

55. The method according to Claim 37, wherein said method comprises the administration of Compound 4 and Carboplatin.

56. The method according to Claim 36, wherein said method comprises the administration of Compound 4 and doxorubicin.

57. The method according to Claim 37, wherein said method comprises the administration of Compound 4 and doxorubicin

58. The method according to Claim 36, wherein said compound of Formula II is selected from the group consisting of

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Azidomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[[[(1,1-Dimethylethoxy)carbonyl]amino]methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-[[[(1,1-Dimethylethoxy)carbonyl]amino]methyl]-4-thiazolyl]-1-methyl-ethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;

20

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;

25

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(pentanoyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(naphthoyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35



[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-[(2-methoxyethoxy)acetyloxy]methyl]-1-methyl-4-thiazolyl]ethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(N-propionylamino)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(3-Acetyl-2,3-dihydro-2-methylene-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, N-oxide;

15

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(methoxymethyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-(phenoxymethyl)-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[(Ethylthio)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Ethoxymethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35

- 5 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2,3,4,6-tetraacetyl-alpha-glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2',3',4',6'-tetraacetyl-beta-glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(6'-acetyl-alpha-glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(p-toluenesulfonyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Bromomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(5-Bromo-2-methyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 35 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Cyanomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-

dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-(Cyanomethyl)-4-thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(1H-imidazol-1-ylmethyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Ethenyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(methoxyimino)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[[ (phenylmethyl) imino] methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Acetyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-oxiranyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(2-iodoethenyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Ethynyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(methylamino)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[[[2-(Dimethylamino)ethyl]amino]methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[(Dimethylamino)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
[[Bis(2-methoxyethyl)amino]methyl]-4-thiazolyl]-1-  
methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-  
4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(4-methyl-1-  
piperazinyl)methyl]-4-thiazolyl]ethenyl]-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-4-[2-(7,11-  
Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-  
dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-  
thiazolecarboxylic acid;

20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-4-[2-(7,11-  
Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-  
dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-  
thiazolecarboxylic acid methyl ester;  
and the pharmaceutically acceptable salts, solvents and  
hydrates thereof.

25 59. A pharmaceutical composition for the pharmaceutical  
treatment of cancer with which comprises at least one  
anti-proliferative agent and a compound of Formula II as  
described in Claim 36, and a pharmaceutically acceptable  
carrier.

60. The composition according to Claim 59 for the treatment of cancerous solid tumors.

61. The composition according to Claim 59 for the treatment of refractory tumors.

62. The composition according to Claim 59 wherein the antiproliferative agent is one or more agent selected from the group consisting of a microtubule-stabilizing agent, a microtubule-disruptor agent, an alkylating agent, an anti-metabolite, epidophyllotoxin, an antineoplastic enzyme, a topoisomerase inhibitor, procarbazine, mitoxantrone, a platinum coordination complex, an anthracycline drug, a cell cycle progression inhibitor, a vinca drug, a mitomycin, a bleomycin, a cytotoxic nucleoside, a taxane, Compound 2, Compound 3, Compound 5, an epothilone, discodermolide, a pteridine drug, a diynene, an aromatase inhibitor and a podophyllotoxin.

63. The composition according to Claim 59, wherein the compound of Formula II is selected from the group consisting of

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Azidomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
 [[[1,1-Dimethylethoxy)carbonyl]amino]methyl]-4-  
 thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-  
 pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-  
 5 dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-[[[1,1-  
 Dimethylethoxy)carbonyl]amino]methyl]-4-thiazolyl]-1-  
 methyl-ethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-  
 10 oxa-13(Z)-cyclohexadecene-2,6-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-(Aminomethyl)-4-  
 thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-  
 pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
 8,8,10,12-tetramethyl-3-[1-methyl-2-[2-  
 [(pentanoyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-  
 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
 8,8,10,12-tetramethyl-3-[1-methyl-2-[2-  
 [(naphthoyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-  
 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
 3-[2-[2-[(2-methoxyethoxy)acetyloxy]methyl]-1-methyl-4-  
 thiazolyl]ethenyl]-8,8,10,12-tetramethyl-4,17-  
 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
 8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(N-  
 propionylamino)methyl]-4-thiazolyl]ethenyl]-4,17-  
 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(3-Acetyl-2,3-dihydro-2-methylene-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, N-oxide;

5

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(methoxymethyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-(phenoxymethyl)-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[(Ethylthio)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Ethoxymethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2,3,4,6-tetraacetyl-alpha-glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2',3',4',6'-tetraacetyl-beta-glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-

35



[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2',3',4',6'-  
tetraacetyl-beta-glucosyloxy)methyl]-4-  
thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-  
5 5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(6'-acetyl-alpha-  
glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-  
10 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(p-  
toluenesulfonyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-  
15 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
(Bromomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
dihydroxy-8,8,10,12-tetramethyl-4,17-  
20 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(5-Bromo-  
2-methyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-  
8,8,10,12-tetramethyl-4,17-  
25 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
(Cyanomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
dihydroxy-8,8,10,12,16-pentamethyl-4,17-  
30 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-(Cyanomethyl)-4-  
thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;

35

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(1H-imidazol-1-ylmethyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Ethenyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(methoxyimino)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[[ (phenylmethyl)imino]methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Acetyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-oxiranyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(2-iodoethenyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Ethynyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(methylamino)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[[2-(Dimethylamino)ethyl]amino]methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[(Dimethylamino)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[[Bis(2-methoxyethyl)amino]methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(4-methyl-1-piperazinyl)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-4-[2-(7,11-Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-thiazolecarboxylic acid;

10

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-4-[2-(7,11-Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-thiazolecarboxylic acid methyl ester

15 and the pharmaceutically acceptable salts, solvents and hydrates thereof.

64. The composition according to Claim 59 wherein the compound of Formula II is selected from ~~the~~ group consisting of  
 20 1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
 25 proliferative agent is Compound 2.

65. The composition according to Claim 59 wherein the compound of Formula II is selected from ~~the~~ group consisting of  
 30 1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 3.

35

66. The composition according to Claim 59 wherein said compound of Formula II is 1S-  
[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
5 dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.

67. The composition according to Claim 59, wherein said  
10 compound of Formula II is 1S-  
[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
15 proliferative agent is Cisplatin.

68. The composition according to Claim 59, wherein said composition comprises Compound 4 and Carboplatin.

20 69. The composition according to Claim 59, wherein said method comprises the administration of Compound 4 and doxorubicin.

70. The composition according to Claim 59, wherein said  
25 method comprises the administration of Compound 4 and CPT-11.